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Original Article

Clinical Discussions in Antithrombotic Therapy Management in Patients With Atrial Fibrillation: A Delphi Consensus Panel

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ABSTRACT

Background: In recent years, direct-acting oral anticoagulants (DOACs) have entered clinical practice for stroke prevention in non-valvular atrial fibrillation or prevention and treatment of venous thromboembolism. However, remaining uncertainty regarding DOAC use in some clinical scenarios commonly encountered in the real world has not been fully explored in clinical trials.

Methods: We report on use of a Delphi consensus process on DOAC use in non-valvular atrial fibrillation patients. The consensus process dealt with 9 main topics: (i) DOACs vs vitamin K antagonists in atrial fibrillation (AF) patients; (ii) therapeutic options for patients with stable

RÉSUMÉ

Contexte : Depuis quelques années, les cliniciens prescrivent des anticoagulants oraux directs (AOD) pour prévenir les accidents vasculaires cérébraux (AVC) chez les patients présentant une fibrillation auriculaire (FA) non valvulaire ou pour prévenir et traiter les thromboembolies veineuses. Cependant, les doutes que suscite encore l'emploi des AOD dans certains contextes courants de la pratique clinique n'ont pas encore été bien explorés dans le cadre des études cliniques.

Méthodologie : Nous avons utilisé la méthode de Delphes, une démarche visant à dégager un consensus, afin d'évaluer le recours aux

In recent years, direct-acting oral anticoagulants (DOACs) have entered the clinical practice of a large group of specialists, such as cardiologists, internists, angiologists, neurologists, hematologists, and geriatricians, to reduce the thromboembolic risk associated with atrial fibrillation (AF) or to prevent or treat venous thromboembolism. Use of DOACs represents a landmark revolution in these fields.

The efficacy and safety of DOACs compared to vitamin K antagonists (VKAs), in terms of both pharmacoeconomics and management of follow-up, have been evaluated. Economic sustainability has been assessed. Rivaroxaban, apixaban, edoxaban (direct factor Xa inhibitors), and dabigatran (a direct thrombin inhibitor) have been tested against the traditional approach in phase III randomized controlled trials (RCTs).[1-4] However, some aspects related to the routine use of DOACs are still doubtful, such as the real-world security and handling of these drugs, the effect on patients adequately anticoagulated with VKAs, the choice of a DOAC after an ischemic stroke, assuming an inappropriate low dose, the long-term treatment

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Ethics Statement: The present research has adhered to the relevant ethical guidelines.

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total time in range treated with vitamin K antagonists; (iii) therapeutic options for patients aged > 85 years; (iv) therapeutic management of hyperfiltering patients; (v) pharmacologic interactions; (vi) therapeutic options in the long-term treatment (prevention) of patients with AF and acute coronary syndrome after the triple therapy; (vii) low doses of DOACs in AF patients; (viii) ischemic stroke in patients inappropriately treated with low doses of DOACs; (ix) management of patients taking DOACs with left atrial appendage thrombosis.

Results: A total of 101 physicians (cardiologists, internists, geriatricians, and hematologists) from Italy expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. Agreement among the respondents of ≥ 66% for each statement was considered consensus. A brief discussion of the results for each topic is also reported.

Conclusions: In clinical practice, there is still uncertainty on DOAC use, especially in elderly, fragile, comorbid, and hyperfiltering patients.

AOD chez des patients présentant une FA non valvulaire. L'étude comprenait 9 thèmes principaux : i) utilisation des AOD et des antagonistes de la vitamine K chez les patients présentant une FA; ii) options thérapeutiques pour les patients traités par un antagoniste de la vitamine K dont l'état se maintient depuis un certain temps dans une plage de valeurs normales; iii) options thérapeutiques pour les patients âgés de plus de 85 ans; iv) prise en charge thérapeutique des patients souffrant d'hyperfiltration; v) interactions pharmacologiques; vi) options thérapeutiques pour le traitement prolongé (préventif) des patients présentant une FA et un syndrome coronarien aigu après une trithérapie; vii) utilisation des AOD à faible dose chez les patients présentant une FA; viii) AVC ischémique chez les patients traités de façon inappropriée par un AOD à faible dose; ix) prise en charge des patients prenant un AOD qui présentent une thrombose de l'appendice auriculaire gauche.

Résultats : Au total, 101 médecins (cardiologues, internistes, gériatres et hématologues) italiens ont exprimé leur degré d'accord avec chacun des énoncés proposés sur une échelle de Likert à 5 points (1 = tout à fait en désaccord; 2 = en désaccord; 3 = moyennement d'accord; 4 = d'accord; 5 = tout à fait d'accord). Une note de 1 ou 2 a été considérée comme un désaccord et une note de 3, 4 ou 5, comme un accord. On considérait qu'il y avait un consensus si 66 % ou plus des répondants étaient d'accord avec l'énoncé. Nous présentons également brièvement les résultats obtenus pour chacun des thèmes.

Conclusions : Dans la pratique clinique, l'emploi des AOD soulève encore des doutes, en particulier chez les patients âgés, fragiles ou présentant des affections concomitantes ou une hyperfiltration.

after a period of triple therapy in patients with AF and acute coronary syndrome (, and the management of left atrial appendage thrombosis. Moreover, clinical practice constantly faces patients who are underrepresented in RCTs, such as elderly, fragile, comorbid, hyperfiltering patients. Further clinical research and phase IV registries are required to fully explore the handling of DOACs in these subgroups.

The need for a consensus conference to discuss these topics, focusing on different perspectives, has become apparent.

Materials and Methods

The Delphi method is frequently used in scientific and medical settings with the aim of reaching consensus within a group of experts, when scientific evidence is absent or conflicting.[5-7] This paper reports on use of the Delphi method to evaluate the consensus on clinical management of DOACs in patients with AF. The process has been structured into 4 phases. In the first phase (May-October 2018), 18 regional roundtables were organized. Participants involved in the treatment of AF (cardiologists, internists, geriatricians, and hematologists) discussed the following main issues regarding DOACs: safety and handling, pharmacologic interactions, use of low doses, and patients' adherence and compliance. In the second phase (November 2018), a board of 6 experts was unanimously identified during the roundtables to provide scientific expertise relating to clinical specialties involved in the treatment of patients with AF. This scientific board drafted a list of statements based on the 6 roundtable discussions. During the third phase (December 2018-January 2019), the list of statements was made available online to the 101 clinicians participating in the regional roundtables. A survey was performed online on a secured survey website (first round), using a web-based survey platform (http://www.consensusdelphinao.it/). The results were evaluated by the scientific board (February 2019). The responses of participants were collected and analyzed prior to 2 final consensus meetings held in Milan (May 29, 2019) and Naples, Italy (June 20, 2019). Results from the first-round vote were presented by the scientific board, and a second-round vote was performed (101 participants) to estimate consensus on the statements that were controversial in the first round. Both rounds of vote were blinded.

Delphi statements

The scientific board defined 9 statements: (i) DOACs vs VKAs in AF patients; (ii) therapeutic options for patients with stable total time in range (TTR) treated with VKAs; (iii) therapeutic options for patients aged more than 85 years; (iv) therapeutic management of hyperfiltering patients; (v) pharmacologic interactions; (vi) therapeutic options in the long-term treatment (prevention) of patients with AF and acute coronary syndrome after the triple therapy; (vii) low doses of DOACs in AF patients; (viii) ischemic stroke in patients inappropriately treated with low doses of DOACs; and (ix) management of patients taking DOACs with left-atrial appendage thrombosis. Participants expressed their level of agreement on each statement by using a 5-point Likert scale: 1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Agreement among the respondents

Statement 1: I maintain that DOACs must be considered as the first choice:						
Level of agreement	1	2	3	4	5	TOTAL
1.1 In patients with CHA_2DS_2-VASc ≥ 2	1	2	7	30	61	101
	3%		97%			100%
1.2 Only in patients with high hemorrhagic risk	44	36	9	5	7	101
	79%		21%			100%
1.3 Only in patients not compliant to VKA therapy	44	29	9	9	10	101
	72%		28%			100%
1.4 In patients with CHA_2DS_2-VASc = 1	18	27	36	11	9	101
	45%		55%			100%

Figure 1. Statement 1. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. CHA2DS2-VASc, congestive heart failure; hypertension age ≥ 75 years; diabetes mellitus; stroke or transient ischemic attack; vascular disease, age 65 to 74 years; sex category; VKA, vitamin K antagonist.

of ≥ 66% for each statement was considered consensus. Votes of ratings 1-2 were considered disagreement, and votes of ratings 3-5 were considered agreement.

Results

The overall response rate in the first round of the Delphi process was 100% (101 responding participants out of 101 total panelists), and that in the second round was also 100% (101 of 101). Of the total of 36 items, positive consensus (shared agreement with the statement) was reached for 10, negative consensus (shared disagreement with the statement) was reached for 12, and consensus was not reached for 14. In particular, statements 2 (item 2.2), 4 (all items), 5 (item 5.2), 6 (item 6.1), and 9 (all items) underwent a second vote, without changing the consensus. Items 7.1 and 8.1 were deleted because they were considered to be incorrect.

Topic 1: DOACs vs VKAs in AF patients (Fig. 1)

The panel fully agreed to consider DOACs the first choice in patients with CHA2DS2-VASc score (congestive heart failure; hypertension age ≥ 75 years; diabetes mellitus; stroke or transient ischemic attack; vascular disease, age 65 to 74 years; sex category) ≥ 2, and not only in patients with high hemorrhagic risk or who were not compliant to VKA therapy. By contrast, no consensus was reached about DOACs as the first choice in patients with CHA2DS2-VASc = 1.

Statement 2: Regarding the patient treated with vitamin K antagonist and with stable total time in range:						
Level of agreement	1	2	3	4	5	TOTAL
2.1 I propose switching to a DOAC because it is superior in terms of safety	6	11	22	29	33	101
	17%		83%			100%
2.2 I consider switching to a DOAC only if requested by the patient	18	42	20	11	10	101
	59%		41%			100%
2.3 I consider switching to a DOAC to further improve the patient's compliance	3	9	22	38	29	101
	12%		88%			100%
2.4 I consider it inappropriate to switch to a DOAC	68	21	5	7	0	101
	88%		12%			100%

Figure 2. Statement 2. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulant.

Statement 3: To patients aged more than 85 years, I administer DOACs:						
Level of agreement	1	2	3	4	5	TOTAL
3.1 At low dose, independent of SmPC criteria, to ensure safety	60	25	10	4	2	101
	84%		16%			100%
3.2 Choosing the dose according to SmPC criteria	0	3	20	9	69	101
	3%		97%			100%
3.3 In case the VKA is difficult to manage and does not ensure adequate safety in terms of bleeding	8	18	32	24	19	101
	26%		74%			100%
3.4 I do not use DOACs in these patients	88	10	2	0	1	101
	97%		3%			100%

Figure 3. Statement 3. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulant; SmPC, summary of product characteristics; VKA, vitamin K antagonist.

Topic 2: Therapeutic options for patients with stable TTR treated with VKAs (Fig. 2)

Positive consensus was reached regarding the switch from VKAs to DOACs in patients with stable TTR, because they are safer and help to further improve compliance, despite the recommendation of the current guidelines of the European Society of Cardiology (ESC).[8] Accordingly, negative consensus was reached about the inappropriateness of switching to a DOAC in these patients. By contrast, no consensus was reached on how to proceed when the switch is requested by the patient.

Topic 3: Therapeutic options for patients aged > 85 years (Fig. 3)

In the setting of elderly patients, there was negative consensus that DOACs either should not be used at all or should be used at low dose, independent of the summary of product characteristics (SmPC) criteria. On the other hand, the panel agreed that the dose should be chosen according to SmPC criteria or in cases in which the VKA is difficult to manage and does not ensure adequate safety in terms of bleeding.

Topic 4: Therapeutic management of hyperfiltering patients (Fig. 4)

Hyperfiltering patients are always a concern in terms of drug doses. Thus, effective use of DOACs in these patients is unlikely. The panel agreed that hyperfiltering subjects treated with DOACs should undergo closer follow-up. By contrast, no consensus was reached on whether there is a clear indication to use DOACs in these patients. Similarly, the panel reached no consensus on use of DOACs dependent on the patient's body mass index or with restrictions to certain molecules.

Statement 4: In hyperfiltering patients, the use of DOACs:						
Level of agreement	1	2	3	4	5	TOTAL
4.1 Is always indicated	8	34	39	11	9	101
	42%		58%			100%
4.2 Must require a closer follow-up than in normofiltering patients	6	18	43	18	16	101
	24%		76%			100%
4.3 Depends on patients' BMI	9	35	38	8	11	101
	44%		56%			100%
4.4 Is indicated only for certain DOACs	15	22	44	6	14	101
	37%		63%			100%

Figure 4. Statement 4. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. BMI, body mass index; DOAC, direct-acting oral anticoagulant.

Statement 5: Regarding pharmacological interactions of DOACs, I think:						
Level of agreement	1	2	3	4	5	TOTAL
5.1 They must be criteria for choosing among DOACs	2	5	20	28	46	101
	7%		93%			100%
5.2 They should be considered in the general evaluation, but are not criteria for choosing	15	37	26	18	5	101
	51%		49%			100%
5.3 Food–drug interactions are not criteria for choosing	14	28	24	15	20	101
	42%		58%			100%

Figure 5. Statement 5. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulant.

Topic 5: Pharmacological interactions (Fig. 5)

The panel fully agreed that pharmacologic interactions are criteria to be used in choosing among DOACs. No consensus was reached about pharmacologic interactions to be considered in the general evaluation, and not as criteria for choosing, or about whether food—drug interactions should be used as criteria in choosing among DOACs.

Topic 6: Therapeutic options in the long-term treatment (prevention) of patients with AF and acute coronary syndrome after triple therapy (Fig. 6)

The long-term treatment after triple therapy for acute coronary syndrome in patients with AF is a matter of debate. Positive consensus was reached that DOAC + a single antiplatelet agent should be administered in patients at high hemorrhagic risk. On the contrary, no consensus was reached about this electing this option independent of the hemorrhagic risk. By contrast, the experts agreed that triple therapy should not be used if the patient is not at high hemorrhagic risk.

Topic 7: Low doses of DOACs in AF patients (Fig. 7)

The panel did not determine that low doses of DOACs are unrelated to the risk of thromboembolic events, but rather fully agreed that they increase the risk of thromboembolic events only if inappropriately prescribed. Negative consensus was reached regarding the indication of low doses to all patients with borderline glomerular filtration rate or aged > 85 years.

Topic 8: Ischemic stroke in patients inappropriately treated with low doses of DOACs (Fig. 8)

Ischemic stroke during DOAC treatment is a rare event. However, when it happens in patients taking an inappropriate low dose, the panel fully agreed that they should continue the same drug, increasing the dose. In addition, negative consensus was reached that no switch should be made to VKAs or to unfractionated heparin/low-molecular-weight heparin. No consensus was reached about changing the DOAC.

Statement 6: In the long-term treatment (prevention) of patients with atrial fibrillation and acute coronary syndrome after triple therapy, I consider it appropriate to administer:						
Level of agreement	1	2	3	4	5	TOTAL
6.1 DOAC + SAPT in patients at high hemorrhagic risk	11	22	21	24	23	101
	33%		67%			100%
6.2 DOAC + SAPT independent of the hemorrhagic risk	18	33	18	12	20	101
	50%		50%			100%
6.3 Triple therapy if the patients are not at high hemorrhagic risk	38	32	14	9	8	101
	69%		31%			100%

Figure 6. Statement 6. Values are n (%), unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulant; SAPT, single antiplatelet therapy.

Statement 7: I think that low doses:						
Level of agreement	1	2	3	4	5	TOTAL
7.1 Are not related to the risk of thromboembolic events	32	38	16	9	6	101
	69%		31%			100%
7.2 Increase the risk of thromboembolic events only if inappropriately prescribed	4	8	19	28	42	101
	12%		88%			100%
7.3 Must be prescribed in all patients with borderline GFR (< 50 mL/min) independent of the criteria reported in SmPC	36	37	17	10	1	101
	72%		28%			100%
7.4 Must be prescribed in all patients aged more than 85 years	39	40	9	8	5	101
	78%		22%			100%

Figure 7. Statement 7. Values are n (%), unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. GFR, glomerular filtration rate; SmPC, summary of product characteristics.

Topic 9: Management of patients taking DOACs with left-atrial appendage thrombosis (Fig. 9)

For cases involving left-atrial appendage thrombosis, the panel did not reach consensus about continuing treatment with the same DOAC vs changing it or switching to a VKA. The experts did agree that unfractionated heparin/low-molecular-weight heparin should not be used.

Discussion

The ESC guidelines (2016) regarding AF suggest that either DOACs or VKAs be used for stroke prevention in patients with a CHA2DS2-VASc score of at least 2 (3 for women) without mechanical heart valves or more than mild mitral stenosis, with a preference for DOACs in naïve subjects (ie, they have never undergone treatment).[8] A meta-analysis[9] focusing on the 4 phase-III RCTs regarding DOACs in AF[1-4] suggests that DOACs have a higher efficacy than VKAs in prevention of stroke and systemic embolism (risk ratio 0.81, 95% confidence interval [CI] 0.73-0.91, $P < 0.0001$), and greater or equal safety in regard to several bleeding endpoints. Accordingly, the panel agreed that DOACs should be considered as a first choice for these patients, independent of bleeding risk. Moreover, given that compliance to VKA treatment is about 50%, DOACs should be considered the first choice to promote adherence to therapy,[10] especially for

Statement 8: In patients taking a DOAC reporting an ischemic stroke due to inappropriate low doses, I think that it is correct:						
Level of agreement	1	2	3	4	5	TOTAL
8.1 To continue the treatment, increasing the dose of the same DOAC	3	5	26	29	38	101
	8%		92%			100%
8.2 To continue the treatment, changing the DOAC	14	38	26	10	13	101
	51%		49%			100%
8.3 To switch to treatment with a VKA	44	45	8	4	0	101
	88%		12%			100%
8.4 To use UFH/LMWH	49	43	6	3	0	101
	91%		9%			100%

Figure 8. Statement 8. Values are n, unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulants; UFH/LMWH, unfractionated heparin/low-molecular-weight heparin; VKA, vitamin K antagonist.

Statement 9: In patients taking a DOAC with left atrial appendage thrombosis, I think that it is appropriate:						
Level of agreement	1	2	3	4	5	TOTAL
9.1 To continue the treatment with the same DOAC	29	37	14	11	10	101
	65%		35%			100%
9.2 To continue the treatment, changing the DOAC	18	21	25	22	15	101
	39%		61%			100%
9.3 To switch to treatment with a VKA	25	27	18	14	17	101
	51%		49%			100%
9.4 To use UFH/LMWH	37	38	17	5	4	101
	74%		26%			100%

Figure 9. Statement 9. Values are n (%), unless otherwise indicated. Physicians that expressed their level of agreement on each statement by using a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = somewhat agree; 4 = agree; 5 = strongly agree). Votes 1-2 were considered to be disagreement; votes 3-5 were considered to be agreement. DOAC, direct-acting oral anticoagulants; UFH/LMWH, unfractionated heparin/low-molecular-weight heparin; VKA, vitamin K antagonist.

once-a-day administration.[11] However, twice-daily dosing may lead to incorrect pill intake.[12] An easier process (ie, once-a-day administration) has been demonstrated to be pivotal in facilitating the start of anticoagulant therapy.[13]

Patients with CHA2DS2-VASc 1 (2 for women) are in a grey zone, owing to lack of data, in which anticoagulation treatment should be considered (ESC recommendation IIaB).[8] In a nationwide Danish study, these cases were found to be at moderate annual risk of thromboembolism: 2.01 (1.70 to 2.36) per 100 person-years.[14] A post-hoc analysis of the **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of **A**trial **F**ibrillation (ORBIT-AF) I & II registries found that the majority (60%-70%) of CHA2DS2-VASc = 0-1 patients are treated with oral anticoagulation. In addition, the absolute risks of death, stroke/transient ischemic attack (TIA), and major bleeding were low among men and women with a CHA2DS2-VASc of 0-1, as well as among women[15] with a CHA2DS2-VASc score of 2. Several factors have to be considered and weighted in this setting in order to identify the antithrombotic approach of choice, including the expected incidence of both thromboembolic stroke and bleeding side effects, their impact in terms of morbidity and mortality, the patient's bleeding risk profile, an accurate stratification of the thromboembolic risk beyond the CHA2DS2-VASc score (eg, renal failure, left-atrial enlargement, left-atrial and its appendage morphology and flow, AF burden), and socioeconomic issues.[16] The panel reached no consensus about this topic.

For patients already taking a VKA, ESC guidelines suggest considering a switch to a DOAC (recommendation IIbA) if TTR is inadequate (despite good adherence) or according to patients' preference (if eligible for DOAC).[8] Given the assumption about greater safety and compliance discussed above,[9-13] the panel agreed that a switch to DOACs should be considered when the TTR is optimal. By contrast, the panel did not reach consensus on using patients' preference to determine whether to switch to DOACs (ie, patient opinion should be considered, but it should not be used as the only criterion for making a choice).

Thromboembolic and bleeding events are increased in the very elderly,[17] with the first prevailing on the second.[18] Accordingly, anticoagulation reduces them in the same group,[17] but it is administered less frequently.[19] In patients treated with a VKA, the hemorrhagic risk increases with age more than the thromboembolic risk.[20] By contrast, age per se is a dose-reduction criterion for only dabigatran and apixaban.[21] Edoxaban also shows stable efficacy and safety in the elderly subgroup.[20] Every DOAC carries a lower risk of intracranial hemorrhage, compared with VKAs, in the elderly.[22] The inappropriate use of low doses of DOACs is associated with a greater risk of ischemic stroke and systemic thromboembolism, and a higher mortality and cardiovascular hospitalization rate, with no safety benefits.[23-26] The panel strongly disagreed with a default use of low doses in the elderly, confirming both the administration of doses according to SmPC indications and the switch from a VKA to a DOAC if the VKA does not ensure adequate safety.

All DOACs are at least partly eliminated by the kidneys, principally dabigatran (80%), so renal function may affect systemic drug exposure, efficacy, and safety. Consequently, renal function needs to be monitored diligently, at least once a year, to detect functional changes in order to adapt the dose.[8,27] In contrast, there is less focus on DOAC efficacy in patients with normal renal function, in whom it could be hypothesized that normal or supranormal filtration may lead to suboptimal effective dosing and therefore suboptimal prevention of thromboembolism. Of note, hyperfiltration or augmented/enhanced renal clearance is a condition characterized by creatinine clearance (CrCl) > 130 mL/min and is typical in critically ill patients.[28,29] In this context, real-world data[30] suggest that dabigatran is less efficacious than warfarin in patients with CrCl > 90 mL/min; rivaroxaban shows a trend toward higher relative rates of stroke and systemic embolism[31] in subjects with CrCl > 95 mL/min; and apixaban carries a higher hazard ratio (HR)[32,33] for first ischemic stroke when CrCl > 80 mL/min. In addition, a box warning from the US Food and Drug Administration and an alert from the

European Medicines Agency have been provided regarding use of edoxaban in patients with CrCl >95 mL/min. Nevertheless, real-world data do not confirm this caution.[34-36] Several exploratory analyses[37] suggested that high-dose edoxaban has a lower relative efficacy for prevention of stroke/systemic embolism, compared with warfarin, at higher levels of renal function (CrCl $\leq$ 50 mL/min: HR 0.87 [95% CI 0.65-1.18]; CrCl > 50-95 mL/min: HR 0.78 [95% CI 0.64-0.96]; CrCl > 95 mL/min: HR 1.36; 95% CI [0.88-2.10]; *P* for interaction = 0.08). However, bleeding rates were lower at all levels of CrCl with edoxaban, so the net clinical outcome was more favorable.[37] Consequently, the panel agreed that caution should be exercised in dealing with this subgroup of patients, reaching consensus that a closer follow-up should be adopted. In particular, in very obese patients, a VKA should be considered.

Treatment with VKAs requires careful consideration of multiple food and drug−drug interactions. Fewer interactions with DOACs have been reported, although it is important to be aware that plasma levels of DOACs are affected[27,38] by drugs that alter the cell efflux transporter P-glycoprotein and/or cytochrome P450. The only DOAC presenting a reduction criterion based on P-glycoprotein inhibitors is edoxaban.[4] European practical guidelines specify different kinds of alerts depending on the specific DOAC−drug interaction, with some contraindications.[27] Accordingly, the panel reached positive consensus regarding drug−drug interactions that should be considered drivers in choosing among DOACs. By contrast, no consensus was reached regarding considering drug−drug interactions in the general evaluation, when they are not in the category of drivers of choice among DOACs, or food−drug interactions as drivers in this choice. The lack of consensus is probably related to the fact that not all interactions merit a mandatory choice.

A total of 5%-8% of patients undergoing percutaneous coronary intervention suffer from AF, and approximately one-third of those affected by AF also have coronary artery disease, so the necessity of triple therapy is frequent in the real world.[39] Antiplatelet therapy is needed to prevent stent thrombosis, and oral anticoagulants are required to prevent stroke; combining the 2 treatments increases bleeding.[40] Triple therapy provides a 3.7-fold increased risk of fatal and nonfatal bleeding compared with warfarin alone.[40] In this field, bleeding is associated with increased mortality, not only in the hospital but also after discharge, regardless of the bleeding site.[41-44] The challenge of balancing the risk of thromboembolism (ie, stroke) and atherothrombotic events (ie, stent thrombosis) with the risk of bleeding lead to the need to clarify the optimal combination regimen in terms of choice of agents, dose, and duration of therapy. The **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) trial comparing triple therapy with warfarin vs clopidogrel + warfarin for 1 year found positive impacts on safety.[45] Following this study, 4 RCTs[46-49] and 2 meta-analyses,[49,50] comparing triple therapy with warfarin to dual therapy with DOAC, confirmed that the combination of a DOAC plus $P2Y_{12}$ inhibitor was associated with less bleeding compared with a VKA plus dual antiplatelet therapy, and that strategies omitting aspirin caused less bleeding, including intracranial hemorrhage, without a significant difference in major adverse cardiac events, compared with strategies including aspirin. However, none of these RCTs was designed to be large enough to detect small but potentially meaningful differences in the incidence of ischemic events. The recent European practical guide on DOACs suggest the possibility of shortening triple therapy from 3 months after acute coronary syndrome to discharge, or lengthening it to 1 year or beyond, according to the individual balance between bleeding and atherothrombotic risk.[27] An initial period of triple therapy is still considered fundamental to avoid early stent thrombosis, followed by personalized therapy according to the patient's characteristics. The panel agreed that therapy should be continued with a DOAC plus a single antiplatelet agent in patients at high hemorrhagic risk, and that this strategy should not be extended to all patients; however, no consensus exists about choosing a DOAC plus independently selecting a single antiplatelet agent for the hemorrhagic risk.

The prescription of a reduced dose of DOACs is regulated by precise criteria, which are different for each drug and for AF and venous thromboembolism contexts.[27] The reduced dose according to the proper criteria aims at providing a plasmatic concentration, and thus clinical results, similar to those of the full dose. Otherwise, an inappropriately reduced dose translates into an insufficient plasmatic concentration of the drug, with a reduced effect. Interestingly, a low plasmatic concentration in patients taking a reduced-dose DOAC is associated with a high risk of thromboembolism.[51] Consequently, real-world data confirm that undertreated patients experience a high risk of ischemic stroke, particularly for apixaban,[23,25,26,52] and cardiovascular hospitalization.[26] The panel agreed that only inappropriately reduced doses of DOACs are related to thromboembolic events, and that the precise criteria of dose reduction must always be followed.

In patients with cardioembolic stroke associated with AF, the risk of early stroke recurrence (within 2 weeks) is between 0.1% and 1.3% per day,[53,54] meaning 4.8% within 48 hours[55] and 7.6%-10% within 90 days (including TIA and systemic embolism).[56,57] Interestingly, only half of such events recur as the same subtype (eg, cardioembolism, large arteries atherosclerosis, small vessel occlusion),[58] and the cardioembolic recurrence is associated with the best survival rate.[58] In the real world, about 32% of patients with AF are treated with an inappropriate dose of DOACs, most often undertreatment.[59] Older and riskier patients more frequently receive a wrong low-dose DOAC without a renal indication for dose reduction.[25] Initiation of an anticoagulant in the first few days after stroke could prevent ischemic stroke recurrence, but it might increase the risk of symptomatic intracranial hemorrhage, including hemorrhagic transformation of the infarct (estimated at about 9% in the first 7 days),[60] leading to clinical uncertainty about when to start anticoagulation. The optimal timing of anticoagulation following an acute ischemic stroke or TIA is unknown.[8] As opposed to the findings regarding aspirin, RCTs to date have failed to produce any evidence supporting the administration of heparin, heparinoids, or low-molecular-weight heparin in patients with acute ischemic stroke and AF within 48 hours from stroke onset.[61-63] Accordingly, the panel strongly disagreed with switching from a low-dose DOAC to heparin. Comparing DOACs to VKAs in this context, explorative data suggest similar efficacy and better safety of DOACs.[64,65] Thus, the

experts disagreed with switching from a low-dose DOAC to a VKA. There is no evidence from RCTs to indicate that one DOAC should be preferred over another or that switching from one DOAC to another is recommended in patients with a history of ischemic stroke undergoing DOAC therapy.[8,27] Recently, Kato et al.,[66] analyzing a small cohort of patients suffering from ischemic stroke while taking a DOAC, found that dabigatran 110 mg tended to be changed to another DOAC, rivaroxaban 15 mg tended to remain unchanged, apixaban 2.5 mg tended to be changed to the standard dose from before the event until discharge.[66] The panel expressed positive consensus that a DOAC should be administered at the standard dose if a lower dose of the same DOAC was inappropriate; they did not reach consensus on whether to switch to another DOAC, in absence of evidence highlighted by the guidelines.[8,27]

Transesophageal echocardiography is the technique of choice over electric cardioversion to search for atrial thrombi if AF lasts for at least 48 hours and the patient has not been taking anticoagulants for at least 3 weeks.[8] VKAs are the anticoagulant of choice in this context,[8] as there are no randomized data on DOAC therapy in the presence of a left atrial appendage (LAA) thrombus. Some case series have examined thrombus resolution in > 95% of cases, with a low but not negligible percentage of persistence and without difference among DOACs.[67-71] Interestingly, more than 40% of patients with LAA thrombosis show persistent clot, despite additional extended uninterrupted anticoagulation, independent of the therapy chosen (ie, DOAC, VKA, change from DOAC to warfarin or vice versa, change among DOACs).[72] On the other hand, some cases are reported about thrombus resolution for (thanks to) the switch to another DOAC.[73,74] Accordingly, the panel did not reach consensus about the best strategy to pursue in the presence of LAA thrombus during DOAC therapy— continue the same DOAC, change to another DOAC, or switch to a VKA. However, they disagreed strongly with switching to heparin.

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Supplementary Material

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